neonates and children up to 18 years of age may be given 20 micrograms/kg of atropine sulfate (to a maximum of 600 micrograms in those aged 1 month and over). It has been suggested that in the presence of bradycardia atropine sulfate should be given several minutes before neostigmine. Glycopyrronium bromide has been used as an alternative to atropine sulfate.

In the treatment of paralytic **ileus** and postoperative **urinary retention**, oral doses of 15 to 30 mg of the bromide, or more usually 500 micrograms of the metilsulfate by subcutaneous or intramuscular injection, have been used.

**Administration in renal impairment.** The dosage of neostigmine may need to be adjusted in patients with renal impairment. The mean serum elimination half-life of 79.8 minutes obtained in patients with normal renal function was found to be prolonged to 181.1 minutes in anephric patients.[1]

1. Cronnelly R, *et al.* Renal function and the pharmacokinetics of neostigmine in anesthetized man. *Anesthesiology* 1979; **51:** 222–6.

**Decreased gastrointestinal motility.** Parasympathomimetics enhance gastric contractions and increase intestinal motility and have been used in conditions associated with decreased gastrointestinal motility (p.1694). Good results have been reported with intravenous neostigmine in the treatment of acute colonic pseudo-obstruction,[1,2] a condition that appears to be due to parasympathomimetic dysfunction. These results have been confirmed in a randomised double-blind study.[3] It has therefore been suggested that parasympathomimetics should be tried before colonic decompression or surgery when conservative management has failed or a rapid resolution is required.[3] Neostigmine has also been used in the treatment of severe constipation due to disrupted intestinal motility.[4,5]

1. Hutchinson R, Griffiths C. Acute colonic pseudo-obstruction: a pharmacological approach. *Ann R Coll Surg Engl* 1992; **74:** 364–7.
2. Stephenson BM, *et al.* Parasympathomimetic decompression of acute colonic pseudo-obstruction. *Lancet* 1993; **342:** 1181–2.
3. Ponec RJ, *et al.* Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med* 1999; **341:** 137–41.
4. Miller LS. Neostigmine for severe constipation with spinal cord lesions. *Ann Intern Med* 1984; **101:** 279.
5. Thurtle OA, *et al.* Intractable constipation in malignant phaeochromocytoma: combined treatment with adrenergic blockade and cholinergic drugs. *J R Soc Med* 1984; **77:** 327–8.

**Local anaesthesia.** Intrathecal neostigmine has been added to spinal local anaesthetics or opioids as an adjunct to prolong regional analgesia and improve haemodynamic stability. A systematic review[1] of studies of such use found that although neostigmine in doses up to 500 micrograms produced a very modest increase in analgesia in the perioperative and peripartum setting, it did not appear to improve haemodynamic stability and the incidence of adverse effects was greatly increased, even at low doses. The disadvantages were felt to outweigh whatever benefits such therapy might have.

1. Ho, KM, *et al.* Use of intrathecal neostigmine as an adjunct to other spinal medications in perioperative and peripartum analgesia: a meta-analysis. *Anaesth Intensive Care* 2005; **33:** 41–53.

**Reversal of neuromuscular blockade.** Anticholinesterases have often been used after surgery to antagonise residual neuromuscular block induced by long-acting competitive neuromuscular blockers. However, there has been continuing debate[1-3] on whether anticholinesterases can be used in reduced doses or even omitted for intermediate-acting blockers such as atracurium and vecuronium and shorter-acting blockers such as mivacurium.

Decreasing the anticholinesterase dose may reduce adverse effects. Although it is not clear whether omitting neostigmine reversal reduces nausea and vomiting,[3,4] it avoids any adverse effects neostigmine may have on gut anastomoses. One commentator[1] considered that the wide variation in recovery time with aminosteroid blockers such as rocuronium was an indication for always using at least a small dose of anticholinesterase when these drugs were used. However, it was suggested that, if the block was being carefully monitored and recovery was established, a reduced dose of 1.25 mg of neostigmine might be preferable after a benzylisoquinolinium blocker such as atracurium or mivacurium. In children, smaller doses of an anticholinesterase could be used, even after an aminosteroid blocker, and after a blocker such as mivacurium, they might not be needed at all.

Others have preferred to reserve neostigmine reversal for cases where it was deemed clinically necessary: in a study[4] using such a protocol, 68% of those receiving rocuronium were given neostigmine, against 10% of those receiving mivacurium.

It has been suggested that because of its shorter duration of action edrophonium might be more suitable than neostigmine to antagonise residual block for neuromuscular blockers with shorter actions and in particular, that edrophonium might be more appropriate than neostigmine for use with mivacurium. Neostigmine inhibits the plasma cholinesterase responsible for the metabolism of mivacurium and its use can in theory delay rather than speed recovery, although in practice there is considered to be little evidence for such an effect.[1] Edrophonium also has lesser effects on the vagus, a more rapid onset of action, and may be associated with a lower incidence of nausea and vomiting than neostigmine.[5] Neostigmine can cause clinically significant neuromuscular blockade if it is given to a patient who has already recovered a large degree of neuromuscular function[6,7] but edrophonium appears not to have this effect.[8] However, the antagonism produced by edrophonium is not adequately and reliably sustained especially after profound block.[9,10]

1. Hunter JM. Is it always necessary to antagonize residual neuromuscular block? Do children differ from adults? *Br J Anaesth* 1996; **77:** 707–9.
2. Fawcett WJ. Neuromuscular block in children. *Br J Anaesth* 1997; **78:** 627.
3. Fuchs-Buder T, Mencke T. Use of reversal agents in day care procedures (with special reference to postoperative nausea and vomiting). *Eur J Anaesthesiol* 2001; **18** (suppl 23): 53–9.
4. Joshi GP, *et al.* The effects of antagonizing residual neuromuscular blockade by neostigmine and glycopyrrolate on nausea and vomiting after ambulatory surgery. *Anesth Analg* 1999; **89:** 628–31.
5. Watcha MF, *et al.* Effect of antagonism of mivacurium-induced neuromuscular block on postoperative emesis in children. *Anesth Analg* 1995; **80:** 713–17.
6. Hughes R, *et al.* Neuromuscular blockade by neostigmine. *Br J Anaesth* 1979; **51:** 568P.
7. Payne JP, *et al.* Neuromuscular blockade by neostigmine in anaesthetized man. *Br J Anaesth* 1980; **52:** 69–75.
8. Astley BA, *et al.* Electrical and mechanical responses after neuromuscular blockade with vecuronium, and subsequent antagonism with neostigmine or edrophonium. *Br J Anaesth* 1987; **59:** 983–8.
9. Caldwell JE, *et al.* Antagonism of profound neuromuscular blockade induced by vecuronium or atracurium: comparison of neostigmine with edrophonium. *Br J Anaesth* 1986; **58:** 1285–9.
10. Mirakhur RK, *et al.* Antagonism of vecuronium-induced neuromuscular blockade with edrophonium or neostigmine. *Br J Anaesth* 1987; **59:** 473–7.

**Snake bite.** The general management of snake bites is discussed on p.2239. Numerous reports from India have claimed benefit for anticholinesterases in the treatment of neurotoxic snake bites but failure to distinguish between cobra and krait bites, lack of controls, and inadequate information about other therapy weaken the claims.[1] However, edrophonium has been shown in 2 double-blind studies to be more effective than placebo[2] and antivenom[3] in the treatment of snake bite due to the Philippine cobra (*Naja naja philippinensis*). Neostigmine has also been reported[4] to have been effective in reversing paralysis in 2 patients bitten by *Micrurus frontalis* (a coral snake). Similarly, another patient made a remarkable recovery when treated with neostigmine after being bitten by an Asiatic cobra (*Naja naja kaouthia*).[5] Anticholinesterases would be expected to be of little value for bites from snakes whose venom contains neurotoxins which act presynaptically, including the Asian krait, the Australian tiger snake, and the taipan[6] and, although beneficial results have been reported in individual patients,[7] overall results are considered to be inconsistent.[2,8] However, it is recommended that a test dose of edrophonium preceded by atropine should be given to patients with neurological signs after a snake bite by any species and if improvement occurs, a longer acting anticholinesterase such as neostigmine can be given.[2,3]

1. Reid HA. Venoms and antivenoms. *Trop Dis Bull* 1983; **80:** 23.
2. Watt G, *et al.* Positive response to edrophonium in patients with neurotoxic envenoming by cobras (Naja naja philippinensis). *N Engl J Med* 1986; **315:** 1444–8.
3. Watt G, *et al.* Comparison of Tensilon and antivenom for the treatment of cobra-bite paralysis. *Trans R Soc Trop Med Hyg* 1989; **83:** 570–3.
4. Vital Brazil O, Vieira RJ. Neostigmine in the treatment of snake accidents caused by Micrurus frontalis: report of two cases. *Rev Inst Med Trop Sao Paulo* 1996; **38:** 61–7.
5. Gold BS. Neostigmine for the treatment of neurotoxicity following envenomation by the Asiatic cobra. *Ann Emerg Med* 1996; **28:** 87–9.
6. Brophy T, Sutherland SK. Use of neostigmine after snake bite. *Br J Anaesth* 1979; **51:** 264–5.
7. Warrell DA, *et al.* Severe neurotoxic envenoming by the Malayan krait Bungarus candidus (Linnaeus): response to antivenom and anticholinesterase. *BMJ* 1983; **286:** 678–80.
8. Trevett AJ, *et al.* Failure of 3,4-diaminopyridine and edrophonium to produce significant clinical benefit in neurotoxicity following the bite of Papuan taipan (Oxyuranus scutellatus carini). *Trans R Soc Trop Med Hyg* 1995; **89:** 444–6.

**Tetrodotoxin poisoning.** For reference to the use of neostigmine in the treatment of tetrodotoxin poisoning caused by eating puffer fish, see under Uses and Administration of Edrophonium Chloride, p.631.

## Preparations

***BP 2008:*** Neostigmine Injection; Neostigmine Tablets;
***USP 31:*** Neostigmine Bromide Tablets; Neostigmine Methylsulfate Injection.

**Proprietary Preparations** (details are given in Part 3)

***Arg.:*** Fadastigmina; Prostigmin; ***Austral.:*** Prostigmin; ***Austria:*** Normastigmin; Prostigmin; ***Belg.:*** Prostigmine; Robinul-Neostigmine; ***Braz.:*** Normastig; Prostigmine; ***Canad.:*** Prostigmin; ***Chile:*** Prostigmine†; ***Cz.:*** Syntostigmin; ***Denm.:*** Robinul-Neostigmin; ***Fin.:*** Glycostigmin; Robinul-Neostigmin; ***Fr.:*** Prostigmine; ***Ger.:*** Neostig; ***Gr.:*** Prostigmine; ***Hong Kong:*** Prostigmin†; ***Hung.:*** Stigmosan; ***India:*** Tilstigmin; ***Indon.:*** Prostigmin; ***Israel:*** Prostigmine†; ***Ital.:*** Intrastigmina; Prostigmina; ***Malaysia:*** Prostigmin†; ***Mex.:*** Prostigmine; ***Neth.:*** Prostigmin; ***Norw.:*** Robinul-Neostigmin; ***Philipp.:*** Prostigmin; ***Pol.:*** Polstigminum; ***Port.:*** Intrastigmina; Prostigmine; ***Spain:*** Prostigmine; ***Swed.:*** Robinul-Neostigmin; ***Switz.:*** Prostigmin; Robinul-Neostigmine; ***Thai.:*** Prostigmin; ***UK:*** Robinul-Neostigmine; ***USA:*** Neostigmine Min-I-Mix; Prostigmin.

**Multi-ingredient:** ***Austria:*** Normastigmin mit Pilocarpin; Pilostigmin Puroptal; ***Ger.:*** Syncarpin-N†.

# Pyridostigmine Bromide *(BAN, rINN)*

Bromuro de piridostigmina; Piridostigmin Bromür; Piridostigmino bromidas; Piridosztigmin-bromid; Pyridostig. Brom.; Pyridostigmiinibromidi; Pyridostigminbromid; Pyridostigmine, bromure de; Pyridostigmini bromidum; Pyridostigminii Bromidum; Pyridostigminium-bromid. 3-Dimethylcarbamoyloxy-1-methylpyridinium bromide.

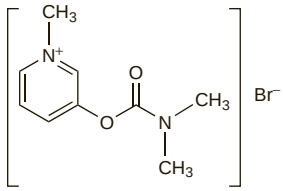
Пиридостигмина Бромид

$C_9H_{13}BrN_2O_2$ = 261.1.

*CAS — 155-97-5 (pyridostigmine); 101-26-8 (pyridostigmine bromide).*

*ATC — N07AA02.*

*ATC Vet — QN07AA02.*



**Pharmacopoeias.** In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
**Ph. Eur. 6.2** (Pyridostigmine Bromide). A white or almost white deliquescent crystalline powder. Very soluble in water and in alcohol. Store in airtight containers. Protect from light.
**USP 31** (Pyridostigmine Bromide). A white or practically white, hygroscopic, crystalline powder, having an agreeable characteristic odour. Freely soluble in water, in alcohol, and in chloroform; practically insoluble in ether; slightly soluble in petroleum spirit. Store in airtight containers.

## Adverse Effects, Treatment, and Precautions

As for Neostigmine, p.631. It has been stated that muscarinic adverse effects occur less frequently with pyridostigmine treatment than with neostigmine.

**Breast feeding.** Pyridostigmine was present in the breast milk of 2 nursing mothers, receiving maintenance therapy for myasthenia gravis, in a concentration between 36 and 113% of that in maternal plasma,[1] but in both cases the dose ingested per kg body-weight by the nursing infant was 0.1% or less of that ingested by the mother. Maternal medication with pyridostigmine should be no obstacle to breast feeding, at least with doses in the range of 180 to 300 mg daily.

On the basis of this study, the American Academy of Pediatrics considers[2] that pyridostigmine is usually compatible with breast feeding.

1. Hardell L-I, *et al.* Pyridostigmine in human breast milk. *Br J Clin Pharmacol* 1982; **14:** 565–7.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 15/02/06)

**Effects on the joints.** Several years after starting oral pyridostigmine bromide 60 mg five times daily, a middle-aged woman had episodes of bilateral arthralgia and hyperalgesia of her hips, knees, toes, and shoulders.[1] Symptoms resolved when pyridostigmine was stopped and rechallenge was positive on several occasions.

1. Rostedt A, Stålberg E. Joint pain and hyperalgesia due to pyridostigmine bromide in a patient with myasthenia gravis. *Neurology* 2004; **62:** 835–6.

**Psychosis.** Postoperative psychosis in a patient with myasthenia gravis who received large doses of pyridostigmine bromide was attributed to bromide intoxication,[1] but this diagnosis has been challenged.[2]

1. Rothenberg DM, *et al.* Bromide intoxication secondary to pyridostigmine bromide therapy. *JAMA* 1990; **263:** 1121–2.
2. Senecal P-E, Osterloh J. Confusion from pyridostigmine bromide: was there bromide intoxication? *JAMA* 1990; **264:** 454–5.

**Renal impairment.** During use of pyridostigmine for the reversal of neuromuscular blockade produced by competitive neuromuscular blockers, pyridostigmine kinetics were not significantly different after renal transplantation in 5 patients compared with those in 5 patients with normal renal function. However, in 4 anephric patients the elimination half-life was significantly in-

creased and the plasma clearance significantly decreased.[1] It appeared that about 75% of the plasma clearance of pyridostigmine depended on renal function.

1. Cronnelly R, *et al*. Pyridostigmine kinetics with and without renal function. *Clin Pharmacol Ther* 1980; **28:** 78–81.

## Interactions

As for Neostigmine, p.632.

## Pharmacokinetics

Pyridostigmine bromide is poorly absorbed from the gastrointestinal tract. It undergoes hydrolysis by cholinesterases and is also metabolised in the liver. Pyridostigmine is excreted mainly in the urine as unchanged drug and metabolites. Pyridostigmine crosses the placenta and very small amounts are distributed into breast milk (see Breast Feeding, above). Penetration into the CNS is poor.

◊ It has been suggested[1] that data from pharmacokinetic studies of pyridostigmine might have varied because of the analytical methods used or inappropriate storage conditions of plasma samples; it was recommended that samples should be acidified and stored at −75°. Mean terminal elimination half-life was 200 minutes in 11 healthy subjects given 60 mg of pyridostigmine by mouth; maximum plasma concentrations were obtained 1 to 5 hours after dosing. The mean terminal elimination half-life after a 4-mg intravenous infusion in 10 of these subjects was 97 minutes.[1] Oral bioavailability was calculated to vary from 11.5 to 18.9%. In an earlier study food did not appear to affect bioavailability but did delay the time taken to achieve peak plasma concentrations.[2] It appears that 75% of the plasma clearance of pyridostigmine depends on renal function.[3] 3-Hydroxy-*N*-methylpyridinium has been identified as one of the 3 metabolites isolated from the urine of patients taking pyridostigmine.[4]

1. Breyer-Pfaff U, *et al*. Pyridostigmine kinetics in healthy subjects and patients with myasthenia gravis. *Clin Pharmacol Ther* 1985; **37:** 495–501.
2. Aquilonius S-M, *et al*. Pharmacokinetics and oral bioavailability of pyridostigmine in man. *Eur J Clin Pharmacol* 1980; **18:** 423–8.
3. Cronnelly R, *et al*. Pyridostigmine kinetics with and without renal function. *Clin Pharmacol Ther* 1980: **28:** 78–81.
4. Somani SM, *et al*. Pyridostigmine in man. *Clin Pharmacol Ther* 1972; **13:** 393–9.

## Uses and Administration

Pyridostigmine is a quaternary ammonium compound that is a reversible inhibitor of cholinesterase activity with actions similar to those of neostigmine (p.632), but is slower in onset and of longer duration. It is given as the bromide.

Pyridostigmine is mainly used in the treatment of myasthenia gravis (p.629) although its use in neonatal myasthenia has declined in favour of neostigmine. It has also been used in the treatment of paralytic ileus. Pyridostigmine is sometimes used to reverse the neuromuscular blockade produced by competitive neuromuscular blockers but is generally considered less satisfactory than neostigmine. It has also been used as prophylaxis against the neuromuscular effects of nerve gas poisoning (below). Pyridostigmine has been used in the management of postoperative urinary retention (p.2180) but has generally been superseded by catheterisation.

For **myasthenia gravis**, total daily oral doses in the UK may range from 300 mg to 1.2 g; however, the *BNF* states that daily doses of 450 mg should not be exceeded in order to avoid receptor downregulation. It also notes that patients receiving pyridostigmine in doses over 360 mg daily may need more aggressive therapy. In the USA, licensed doses are somewhat higher, ranging up to 1.5 g daily.

The dose should be divided throughout the day and, if necessary, the night, according to response; larger portions of the total daily dose may be given at times of greater fatigue.

A suggested oral dose in the USA for children is 7 mg/kg daily in 5 or 6 divided doses. An alternative regimen used in the UK is an initial dose of 30 mg for children under 6 years or 60 mg for those aged 6 to 12 years. This is increased gradually by increments of 15 to 30 mg daily until a satisfactory response is obtained, which is usually within the dosage range of 30 to 360 mg daily.

Pyridostigmine has also been given as modified-release tablets, usually once or twice daily but these offer less flexibility of dosage. If necessary it has also been given by intramuscular injection or in severe cases by very slow intravenous injection. However, the intravenous route is hazardous and, if used, atropine must be available to counteract any severe muscarinic reactions.

In the treatment of neonatal myasthenia doses in the range of 50 to 150 micrograms/kg by intramuscular injection or 5 to 10 mg orally (30 to 60 minutes before feeds) have been given every 4 to 6 hours. Alternatively, oral doses may be based on neonatal weight: in the UK, the *BNFC* recommends an initial dose of 1 to 1.5 mg/kg, increased gradually to a maximum of 10 mg and repeated throughout the day. Treatment is rarely needed beyond 8 weeks of age.

To **reverse neuromuscular blockade** produced by *competitive neuromuscular blockers*, doses of 10 to 20 mg have been given intravenously, with or preceded by atropine sulfate 0.6 to 1.2 mg to counteract any muscarinic effects. Glycopyrronium bromide has been used as an alternative to atropine.

In the USA pyridostigmine is licensed for prophylaxis against the neuromuscular effects of the nerve gas poison *soman* in military combat use only; the recommended oral dose is 30 mg every 8 hours started at least several hours before exposure to soman. If nerve gas poisoning occurs, pyridostigmine should be stopped and the patient should be treated with atropine and pralidoxime immediately.

In the treatment of paralytic **ileus** and postoperative **urinary retention** pyridostigmine bromide has been given in oral doses of 60 to 240 mg.

**Decreased gastrointestinal motility.** Parasympathomimetics such as pyridostigmine enhance gastric contractions and increase intestinal motility; they have been used in conditions associated with decreased gastrointestinal motility (p.1694).

Pyridostigmine, generally in doses of 60 mg up to 3 times daily, has been used to relieve severe constipation in patients with impaired intestinal motility due to Parkinson's disease.[1]

1. Sadjadpour K. Pyridostigmine bromide and constipation in Parkinson's disease. *JAMA* 1983; **249:** 1148.

**Growth hormone deficiency.** Although the value of stimulated growth hormone secretion tests in children has been questioned (see Growth Retardation, p.1798), pyridostigmine with somatorelin has been found to be a potent and reproducible test for distinguishing adults with severe growth hormone deficiency from normal subjects.[1] However, the combination is not effective in patients over 55 years of age,[2] and somatorelin with arginine is generally preferred where an alternative to the gold standard of the insulin-tolerance test is required.[1]

1. Ghigo E, *et al*. Diagnostic and therapeutic uses of growth hormone-releasing substances in adult and elderly subjects. *Baillieres Clin Endocrinol Metab* 1998; **12:** 341–58.
2. Vierhapper H, *et al*. The use of the pyridostigmine growth hormone-releasing hormone stimulation test to detect growth hormone deficiency in patients with pituitary adenomas. *Metabolism* 2002; **51:** 34–7.

**Nerve gas poisoning.** Pyridostigmine has been used prophylactically to protect soldiers against attack with nerve gas agents (p.2351) that inhibit acetylcholinesterase.[1] Pyridostigmine binds reversibly to acetylcholinesterase and provides a protected store from which acetylcholinesterase is later released.[1-3] Prophylaxis with pyridostigmine greatly enhances the efficacy of treatment with atropine and pralidoxime against exposure to *soman* but it is not effective alone and may not be uniformly effective against other nerve agents.[1] Giving 30 mg of pyridostigmine every 8 hours provides the optimum level of protection[2] and, although adverse effects are common at this dosage, the performance of military duties is not impaired.[4] However, neurological symptoms in veterans suffering the so-called Gulf War Syndrome appear to be more common in those who reported exposure to a range of potentially toxic substances which include pyridostigmine.[5] It has been suggested that these symptoms may be evidence of organophosphate-induced polyneuropathy resulting from exposure to a combination of organophosphorus compounds and other cholinesterase inhibitors such as pyridostigmine.[6] A study in *hens*[7] (a species susceptible to anticholinesterases) has also found symptoms of enhanced neurotoxicity when pyridostigmine, the insect repellent diethyltoluamide, and the pyrethroid insecticide permethrin were used together.

1. United States Army. *Medical management of chemical casualties handbook*, 3rd ed. Aberdeen, Maryland: Medical Research Institute of Chemical Defense; 1999. Also available at: http://www.brooksidepress.org/Products/OperationalMedicine/DATA/operationalmed/Manuals/RedHandbook/001TitlePage.htm (accessed 15/02/06)
2. Ministry of Defence. *Medical manual of defence against chemical agents*. London: HMSO, 1987. (JSP312).
3. Anonymous. Prevention and treatment of injury from chemical warfare agents. *Med Lett Drugs Ther* 2002; **44:** 1–4.
4. Keeler JR, *et al*. Pyridostigmine used as a nerve agent pretreatment under wartime conditions. *JAMA* 1991; **266:** 693–5.
5. The Iowa Persian Gulf Study Group. Self-reported illness and health status among gulf war veterans: a population-based study. *JAMA* 1997; **277:** 238–45.
6. Haley RW, Kurt TL. Self-reported exposure to neurotoxic chemical combinations in the gulf war: a cross-sectional epidemiologic study. *JAMA* 1997; **277:** 231–7.
7. Abou-Donia MB, *et al*. Neurotoxicity resulting from coexposure to pyridostigmine bromide, DEET, and permethrin: implications of gulf war chemical exposure. *J Toxicol Environ Health* 1996; **48:** 35–56.

**Orthostatic hypotension.** Pyridostigmine has been investigated in the treatment of orthostatic hypotension (p.1530). A review[1] of 4 single-dose studies and a follow-up survey (involving a total of 106 patients and generally reporting an improvement in haemodynamic measurements) concluded that there was insufficient long-term data to support the routine use of pyridostigmine in the treatment of orthostatic hypotension.

1. Gales BJ, Gales MA. Pyridostigmine in the treatment of orthostatic intolerance. *Ann Pharmacother* 2007; **41:** 314–18.

**Post-poliomyelitis syndrome.** Although pyridostigmine has been reported[1] in some patients to reduce fatigue associated with post-poliomyelitis syndrome a double-blind placebo-controlled study failed to find any benefit.[2] Doses used[3] have included 30 mg daily increased gradually to about 60 mg three times daily but adverse effects are common.

1. Trojan DA, Cashman NR. Anticholinesterases in post-poliomyelitis syndrome. *Ann N Y Acad Sci* 1995; **753:** 285–95.
2. Trojan DA, *et al*. A multicenter, randomized, double-blinded trial of pyridostigmine in postpolio syndrome. *Neurology* 1999; **53:** 1225–33.
3. Thorsteinsson G. Management of postpolio syndrome. *Mayo Clin Proc* 1997; **72:** 627–38.

## Preparations

***BP 2008:*** Pyridostigmine Tablets;
***USP 31:*** Pyridostigmine Bromide Injection; Pyridostigmine Bromide Syrup; Pyridostigmine Bromide Tablets.

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Mestinon; Piridos; ***Austral.:*** Mestinon; ***Austria:*** Mestinon; ***Belg.:*** Mestinon; ***Braz.:*** Mestinon; ***Canad.:*** Mestinon; ***Chile:*** Mestinon; ***Cz.:*** Mestinon; ***Denm.:*** Mestinon; ***Fin.:*** Mestinon; ***Fr.:*** Mestinon; ***Ger.:*** Kalymin; Mestinon; ***Gr.:*** Mestinon; ***Hong Kong:*** Mestinon; ***Hung.:*** Mestinon; ***India:*** Distinon; ***Indon.:*** Mestinon; ***Irl.:*** Mestinon; ***Israel:*** Mestinon; ***Ital.:*** Mestinon; ***Malaysia:*** Mestinon; ***Mex.:*** Mestinon; ***Neth.:*** Mestinon; ***Norw.:*** Mestinon; ***NZ:*** Mestinon; ***Philipp.:*** Mestinon; ***Pol.:*** Mestinon; ***Port.:*** Mestinon; ***Rus.:*** Kalymin (Калимин); ***S.Afr.:*** Mestinon; ***Singapore:*** Mestinon; ***Spain:*** Mestinon; ***Swed.:*** Mestinon; ***Switz.:*** Mestinon; ***Thai.:*** Mestinon; ***Turk.:*** Mestinon; ***UK:*** Mestinon; Nerve Agent Pre-Treatment Tablet Set LIA1; ***USA:*** Mestinon; ***Venez.:*** Mestinon.

but systemic chemotherapy is the treatment of choice.[1-3,5,6] The main combination regimens use a vinca alkaloid and bleomycin, with or without doxorubicin.[2,3] Liposomal formulations of doxorubicin and daunorubicin have produced response rates of 40-85%, and may be less toxic than conventional chemotherapy;[2,3,8] it has been suggested that a liposomal anthracycline is the drug of choice in extensive disease.[1,2,5-7] Paclitaxel is also used as a single agent in advanced disease.[2,3,7,8] However, although highly effective, doses may need to be reduced if given to patients taking HAART because of the risk of drug interactions.[5,7] Although data are limited, docetaxel may be a reasonable alternative.[7] Some response has also been reported for oral etoposide.[1]

Control of Kaposi's sarcoma has been reported in a few patients given high-dose intramuscular chorionic gonadotrophin, but tumour regression ceased and regrowth occurred when dosage was reduced or withdrawn.[9] Further reports of intralesional or systemic use have included partial remissions and disease stabilisation, as well as no effect or disease progression. The reasons for these contradictory results are unclear, but they may be due to variability in chorionic gonadotrophin preparations, which contain a mixture of biological contaminants. A cytotoxic ribonuclease and the degradation product of the β-hCG subunit have been proposed as active contaminants against Kaposi's sarcoma, but other contaminants may stimulate the tumour.[10] Other lines of investigation include the use of sulfated polysaccharide peptidoglycans, imatinib, other inhibitors of angiogenesis including thalidomide, and the retinoids.[1,5-8]


1. Antman K, Chang Y. Kaposi's sarcoma. *N Engl J Med* 2000; **342:** 1027–38.
2. Mitsuyasu RT. Update on the pathogenesis and treatment of Kaposi sarcoma. *Curr Opin Oncol* 2000; **12:** 174–80.
3. Hermans P. Opportunistic AIDS-associated malignancies in HIV-infected patients. *Biomed Pharmacother* 2000; **54:** 32–40.
4. Stallone G, *et al.* Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *N Engl J Med* 2005; **352:** 1317–23.
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***SOFT-TISSUE SARCOMA.*** Soft-tissue sarcomas are a varied group of malignant tumours that originate from mesenchymal stem cells residing in muscle, fat, or connective tissue,[1,2] and whose subtypes vary in terms of prognosis and response to different treatments.[3] The majority of soft-tissue sarcomas occur in the limb or limb girdle; some occur within the abdomen (retroperitoneal), in the head or neck, or in the gastrointestinal tract.[4,5] Patients have a 5-year survival rate of about 50 to 60%;[4] survival in those with extremity sarcomas is better than that in patients with retroperitoneal sarcomas.[2] Tumours often metastasise to the lung; those arising in the abdomen metastasise to the liver and peritoneum.[4]

**Rhabdomyosarcoma** is the commonest soft-tissue sarcoma in childhood, and is thought to arise from progenitor cells for skeletal muscle. The most frequent sites are the head and neck, genito-urinary tract, and extremities. Some genetic disorders are associated with rhabdomyosarcoma.[6,7] All patients are presumed to have micrometastatic disease at diagnosis; histologically the most common types are embryonal, which occurs at an earlier age, and alveolar, which is more common in adolescents.[7]

The **gastrointestinal stromal tumours** (GISTs) are soft-tissue sarcomas arising in the gastrointestinal tract, most commonly in the stomach and small bowel.[4,8,9] Symptoms may include abdominal pain, anorexia, weight loss, haemorrhage, changes in bowel movements, bowel obstruction, or perforation. Patients with liver metastases may have oedema of the lower extremity, ascites, or jaundice.[10] Spread to the lungs and other locations is seen only in advanced cases.[4]

Surgery is the primary **therapy** for soft-tissue sarcomas,[1,2,4,8] and may be curative for localised disease.[5,11] Radiotherapy, as external-beam therapy or brachytherapy, may be given with surgery, or alone if surgery is inappropriate or declined by the patient.[5] Radiation may be given pre-operatively, during surgery, or postoperatively;[1] optimal timing is unclear.[5,8] Similar rates of local control and progression-free survival have been reported for pre- and postoperative radiotherapy, although pre-operative treatment has been associated with a greater incidence of wound complications, especially in lower extremity tumours.[4] Postoperative radiation can cause acute and delayed bowel toxicity in those with retroperitoneal tumours, and significant toxicity has occurred with the use of brachytherapy, especially when used in the upper abdomen.[2]

Surgery and/or radiotherapy may be combined with chemotherapy. Pre-operative chemotherapy may allow for more efficient resection of the tumour.[1,8] The use of postoperative chemotherapy is controversial,[5,8] except for some tumours such as extraosseous Ewing's sarcoma or rhabdomyosarcoma. For these tumours, combinations of vincristine, dactinomycin, doxorubicin, cyclophosphamide, ifosfamide, or etoposide form the basis of most regimens.[5-8]

For those with unresectable or metastatic disease, chemotherapy may be palliative; ifosfamide and doxorubicin are routinely used in this setting.[5] These may be used as single agents or in combination; other acceptable single agent choices are dacarbazine, gemcitabine, or liposomal doxorubicin.[4] Data support the use of adjuvant doxorubicin-based chemotherapy to improve disease-free survival;[12] however, overall survival is not improved. For palliative treatment in advanced soft-tissue sarcoma, a systematic review[13] concluded that combination chemotherapy did not significantly increase survival rates compared with single-agent doxorubicin. A retrospective analysis[14] found that, in patients with high-risk disease, clinical benefits of doxorubicin-based chemotherapy were not sustained beyond 1 year. There is no consensus on the best second-line chemotherapy regimen for patients with metastatic disease refractory to doxorubicin- or ifosfamide-based regimens.[2,3] Dose-intensified combination regimens, with colony-stimulating factor support, have been investigated as adjuvant therapy[15] and in advanced disease;[16] although both these studies found a delay in disease progression, a beneficial effect on overall survival was only found in the former. Intensive combination chemotherapy benefited a subgroup of children with metastatic rhabdomyosarcoma and fewer than 2 unfavourable risk factors, in terms of event-free survival and overall survival. However, most patients have more than 2 risk factors; these patients should be considered for novel first-line therapies. No evidence was found for improved outcome after consolidation therapy with high-dose melphalan and autologous bone marrow or peripheral-blood stem cell rescue.[17] Response to topotecan has been reported in a study of metastatic rhabdomyosarcoma,[18] and trabectedin has shown some activity in advanced soft-tissue sarcomas.[3,5] Tasonermin and melphalan can be used together for isolated limb perfusion of unresectable soft-tissue sarcomas, but severe toxicity may limit use of this regimen. Potential salvage therapy options after failure of first-line therapy include paclitaxel, docetaxel, gemcitabine, trofosfamide, temozolomide, and various combinations thereof.[3]

Surgery is used for localised, resectable disease arising in the gastrointestinal tract, although this does not routinely cure GISTs; median time to recurrence after resection is about 2 years. Adjuvant imatinib is under investigation in this setting. Imatinib produces durable clinical benefit and objective responses in most patients with GISTS, including those with metastatic or unresectable disease. If the tumour responds to imatinib, surgical resection may be indicated. In patients with imatinib-resistant GIST, or who experience life-threatening adverse effects such as hepatotoxicity and fluid retention with imatinib, sunitinib may be considered.[4,8,9,19]


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## Aclarubicin *(BAN, USAN, rINN)*

Aclacinomycin A; Aclarubicina; Aclarubicine; Aclarubicinum; Aklarubicin; Aklarubisiini; Aklarubisin; NSC-208734. Methyl (1*R*,2*R*,4*S*)-4-(*O*-{2,6-dideoxy-4-*O*-[(2*R*,6*S*)-tetrahydro-6-methyl-5-oxopyran-2-yl]-α-L-*lyxo*-hexopyranosyl}-(1→4)-2,3,6-trideoxy-3-dimethylamino-L-*lyxo*-hexopyranosyloxy)-2-ethyl-1,2,3,4,6,11-hexahydro-2,5,7-trihydroxy-6,11-dioxonaphthacene-1-carboxylate.

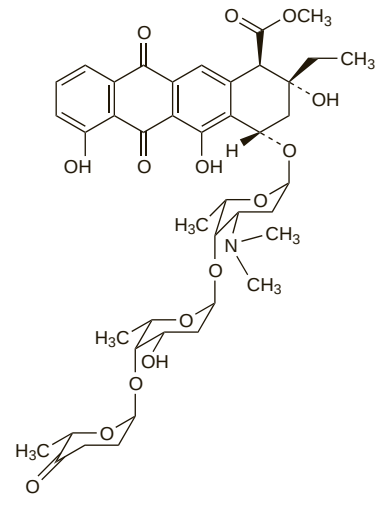
Акларубицин

$C_{42}H_{53}NO_{15}$ = 811.9.

*CAS — 57576-44-0.*

*ATC — L01DB04.*

*ATC Vet — QL01DB04.*



**Description.** Aclarubicin is an anthracycline antineoplastic antibiotic isolated from *Streptomyces galilaeus*.

## Aclarubicin Hydrochloride *(BANM, rINNM)*

Aclarubicine, Chlorhydrate d'; Aclarubicini Hydrochloridum; Hidrocloruro de aclarubicina.

Акларубицина Гидрохлорид

$C_{42}H_{53}NO_{15}$,HCl = 848.3.

*CAS — 75443-99-1.*

*ATC — L01DB04.*

*ATC Vet — QL01DB04.*

**Pharmacopoeias.** In *Jpn*.

**Stability.** In a study of the stability of anthracycline antineoplastic agents in 4 infusion fluids—glucose 5%, sodium chloride 0.9%, lactated Ringer's injection, and a commercial infusion fluid—stability appeared to be partly related to pH; aclarubicin was